Assessment of Cardiovascular Disease after Hypertensive Pregnancy Disorders

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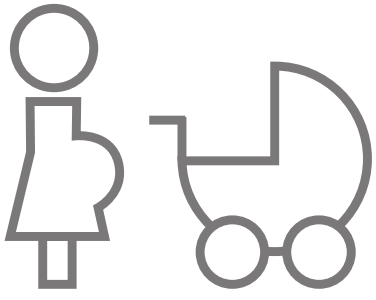

CHAPTER 2

Systematic review and metaanalysis on nonclassic cardiovascular biomarkers after hypertensive pregnancy disorders

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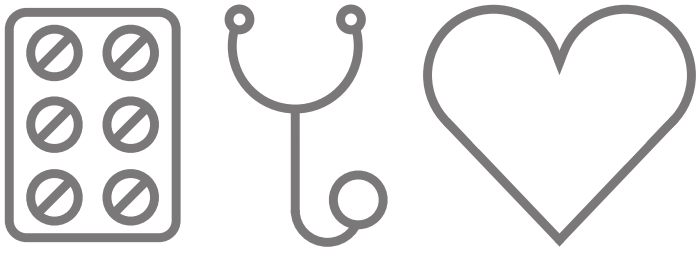


ABSTRACT

Objective: The aim of this study was to investigate which nonclassic cardiovascular biomarkers are associated with persistent endothelial dysfunction after pregnancy in women with a history of hypertensive pregnancy disorders compared with women with uncomplicated pregnancies.

Study design: This was a systematic review and metaanalysis of observational studies. A search was performed in PubMed, Embase, Cochrane, and Cinahl including articles from inception to Feb. 27, 2013. Included were cohort studies and case-control studies. Cases were women with a history of hypertension in pregnancy, control subjects were women with a history of uncomplicated pregnancies. Of the 3136 found, 21 studies on 16 nonclassic cardiovascular biomarkers are described in this review; 12 studies on 5 biomarkers were included in the metaanalysis.

Results: Women with a history of hypertensive pregnancy disorders had a higher homocysteine level compared with women with a history of uncomplicated pregnancies (5 studies; pooled mean difference, 0.77 ng/mL; 95% confidence interval, 0.27e1.26; $P < .01$). For the other nonclassic cardiovascular biomarkers including markers in areas of inflammation, thrombosis, and angiogenesis, we found no significant differences.

Conclusion: This review and metaanalysis showed that women with a history of hypertensive pregnancy disorders have higher homocysteine levels compared to women with a history of uncomplicated pregnancies. These data suggest persistent endothelial alteration after pregnancies complicated by hypertensive disorders.

INTRODUCTION

Cardiovascular disease is the leading cause of death in women in the Western world [1]. Cardiovascular disease manifests itself different between men and women; diagnostic tools in women are less sensitive and specific. Therefore, it is of additional value to identify specific risk factors for cardiovascular disease in women [2-5] For women, preeclampsia has been suggested as a specific risk factor for cardiovascular disease later in life [6,7].

Hypertensive disorders in pregnancy are hypothesized to act as a stress test for cardiovascular disease later in life [8]; women who fail this stress test by developing hypertensive pregnancy disorders have an increased cardiovascular risk, which will become apparent during pregnancy. Both disorders, hypertensive pregnancy disorders and cardiovascular disease later in life, share a common pathophysiologic pathway [9] of endothelial dysfunction.

Recently a review on classic cardiovascular biomarkers showed higher levels of glucose, insulin, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and microalbumin and lower levels of high-density lipoprotein cholesterol in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies [10]. These biochemical cardiovascular risk markers are predictors for cardiovascular disease later in life and might identify high-risk young women early enough to benefit from screening and intervention.

In addition to classic cardiovascular biomarkers, there is a wide variety of nonclassic cardiovascular biomarkers associated with endothelial dysfunction. These latter mentioned biomarkers might be more associated with future risk of cardiovascular disease and therefore might give options for preventive interventions [11-13].

In this systematic review and metaanalysis, we focus on 16 nonclassic cardiovascular biomarkers associated with persistent endothelial dysfunction, including inflammation (intercellular adhesion molecule [ICAM], vascular cell adhesion molecule [VCAM], interleukin-6 [IL-6], interleukin-10 [IL-10], and E-selectin), thrombosis (homocysteine, Von Willebrand factor [VWF], fibrinogen, fibronectin, endothelin, D-dimer, plasminogen activator inhibitor-1 [PAI-1], tissue plasminogen activator [tPA]), and angiogenesis (vascular endothelial growth factor [VEGF], soluble Fms-like tyrosine kinase-1 [sFLT- 1], and tumor necrosis factor alpha ([TNF-a]).

Previous research suggests that these cardiovascular biomarkers could be useful in prediction, identification, and assessment of hypertensive pregnancy disorders, especially preeclampsia [14,15]. Because cardiovascular disease and hypertensive pregnancy disorders share a (partly) common pathophysiology, we used these biomarkers in our search for this systematic review and metaanalysis.

The aim of this study was to investigate whether nonclassic cardiovascular biomarkers are associated with persistent endothelial dysfunction after pregnancy in women with a history of hypertensive pregnancy disorders compared to women who have had uncomplicated pregnancies.

MATERIALS AND METHODS

Definitions

Hypertensive pregnancy disorders include gestational hypertension, preeclampsia, superimposed preeclampsia, and eclampsia. Gestational hypertension was defined according to the International

Society for the Study of Hypertension in Pregnancy criteria as diastolic blood pressure of 90 mmHg or greater measured on 2 occasions at least 6 hours apart in a woman who was normotensive at the start of pregnancy until week 20 of gestational age [16].

Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy criteria: onset of a blood pressure exceeding 140/90mmHg with proteinuria greater than 0.3 g per 24 hours after 20 weeks' gestation [16]. Severe preeclampsia was defined as a blood pressure exceeding 160/110 mmHg or proteinuria greater than 5 g per 24 hours, or both [16]. Eclampsia was defined as the presence of seizures [16,17]. Superimposed preeclampsia was defined as preexisting hypertension with new onset proteinuria greater than 0.3 g per 24 hours after 20 weeks' gestation.

Sources

We searched PubMed, Embase.com, Cochrane Library (via Wiley), and Cinahl (via EBSCO) (J.C.F.K., R.H.J.O., and S.V.) from inception to Feb. 27, 2013. The following search terms with synonyms were used: gestational hypertension, preeclampsia, and eclampsia.

The search on nonclassic cardiovascular biomarkers in the area of inflammation included the following terms with synonyms: ICAM, VCAM, IL-6, IL-10, and E-selectin. The search on nonclassic cardiovascular biomarkers in the area of thrombosis included the following terms with synonyms: homocysteine, VWF, fibrinogen, fibronectin, endothelin, D-dimer, PAI-1, and tPA. The search on nonclassic cardiovascular biomarkers in the area of angiogenesis included the following terms with synonyms: VEGF, sFLT-1, and TNF-a. The search for study type included the following terms with synonyms: systematic reviews, metaanalyses, cohort studies and case-control studies. The choice of biochemical markers was based on the knowledge of their role in hypertensive disorders in pregnancy and suspected endothelial activation.

Study selection

We included case-control studies and cohort studies. Further inclusion criteria hold cases described in the articles had to be women with a history of hypertensive pregnancy disorder by previous mentioned definition, control subjects had to be women with a history of uncomplicated pregnancies, the articles should describe measurements in blood samples of 1 of the nonclassic cardiovascular biomarkers as described above, and blood sample should be drawn more than 6 weeks after delivery. There were no limitations made on publication date or patients sample size.

We excluded studies without the definitions of gestational hypertension or (pre)eclampsia or without baseline criteria of the study population mentioned above. Studies that included superimposed preeclampsia were excluded from this review.

Two reviewers (S.V., W.H.) screened the title, abstract and key words (**figure 1**). All titles were screened by the 2 reviewers (S.V., W.H.). If the title was not specific enough for decision on inclusion or exclusion, we reviewed the abstract according to the following criteria: case control or cohort study and blood samples drawn after pregnancy complicated by hypertensive disorders. No exclusions were made on publication date or language of article. If a reference was potentially eligible, a full-text article was scored using a scoring list conducted by the reviewers (S.V.,W.H., C.J.M.d.G.) to assess the article's quality.

Explicit definitions of gestational hypertension and (pre)eclampsia, parity, mean gestational age, preterm or term pregnancy, number of cases and controls included, follow-up time, and adequate information about blood collection and blood analysis (i.e. if blood samples were taken sober) were required for inclusion in this systematic review. During the comparison of these scoring lists by the reviewers (S.V., W.H.), any inconsistencies were resolved by discussion with a third reviewer (C.J.M.d.G.).

Outcomes of interest

Outcomes were differences in nonclassic cardiovascular biomarkers, measured after pregnancy, between women with a history of hypertensive pregnancy disorders and women with a history of uncomplicated pregnancies. Nonclassic cardiovascular biomarkers found in case-control and cohort studies were numerous (**table 1**).

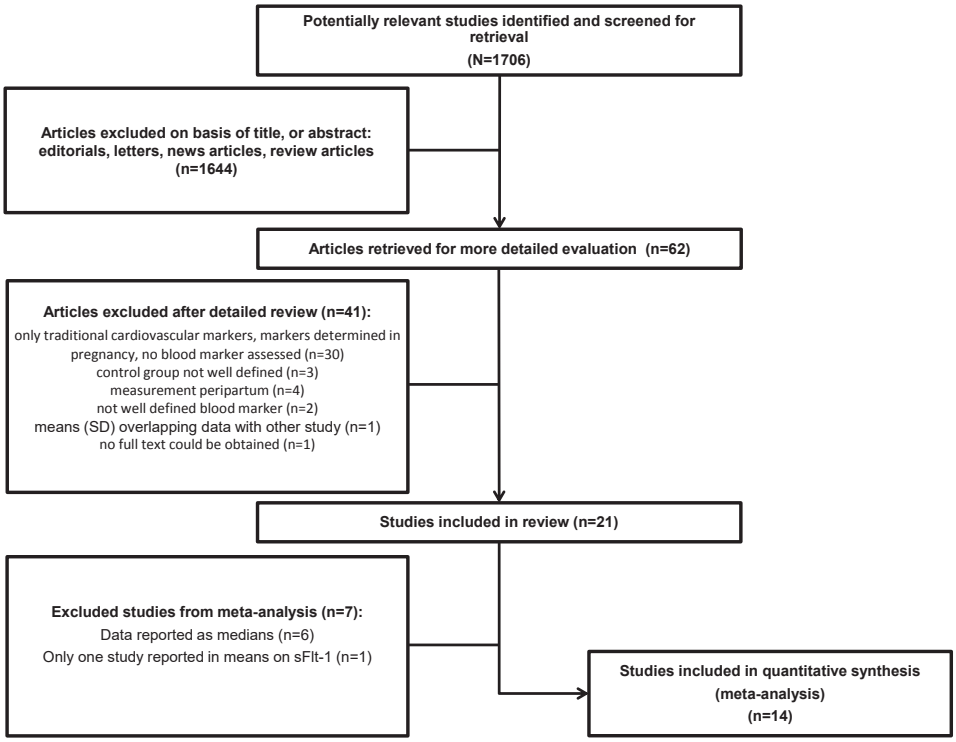


Figure 1.

In this review we describe a specific selection of nonclassic cardiovascular biomarkers (n = 16), ICAM, VCAM, IL-6, IL-10, E-selectin, homocysteine, VWF, fibrinogen, fibronectin, endothelin,

D-dimer, PAI-1, tPA, VEGF, sFLT-1, and TNF-a. Only if 3 or more studies reported on a nonclassic biomarker and reported outcome values as means ± SEM or SD, we preformed a metaanalysis including the nonclassic biomarker. If studies reported values as medians (range/interquartile range) or if less than 3 studies reported on the nonclassic biomarker, we described the nonclassic biomarker separately.

Data synthesis

We used Review Manager 5.0 (Cochrane Collaboration, Oxford, UK) for statistical analyses. Outcomes were reported as continuous data and analyzed using a mean difference. Raw numbers were used from each study, as adjustments for confounding effects varied among the different studies. Weighting of studies in the metaanalyses was calculated on the basis of the inverse variance of the study. The random effects model was chosen because a clinical and statistical heterogeneity was expected among the studies. We used forest plots to visualize data and assessed heterogeneity using the I2 test [18]. For all effect estimates, a value of $P < .05$ indicated statistical significance.

RESULTS

Literature identification and study quality

The initial search produced 4995 articles: PubMed 1775 articles, Embase 2757 articles, Cinahl 260 articles, and Cochrane 119 articles. After removing duplicates of references that were selected from more than 1 database, 3136 articles remained. After screening the titles and abstracts, we retrieved 73 articles for detailed evaluation of the full text. As described in the **figure 1**, we included 21 articles of these 73 in this review. For the metaanalyses we included 12 articles that reported on 5 different nonclassic cardiovascular biomarkers. The other nonclassic cardiovascular biomarkers will be described separately.

Study characteristics

The studies included in this review were published from 1994 to 2012. Study characteristics are shown in the **table 1**. Data collection of studies in this review was prospective design in 15 studies (71%) [20-23,25,27-29,32-37,39]. Six studies (29%) were designed as cohort studies [19,25,26,30,31,38] and 15 (71%) were case control studies [20-24,27-29,32-37,39].

In 1 study (5%), only women with a history of pregnancy induced hypertension were included [30]; 2 studies (9%) included women with a history of pregnancy induced hypertension and preeclampsia [25,31], and 18 studies (86%) included women with a history of preeclampsia [19-24,27-30,32-39].

In 11 studies (52%), both nulliparous and multiparous women were included [19,20,22-24,28,30,31,34,37,39]; in 7 other studies (32%), only nulliparous women were included [25-27,29,32,33,36]. We included 3 studies (14%) in which parity was not described [21,35,38]. In 3

studies (14%), women were included only after a term pregnancy [19,30,31]; in 7 studies (33%), women who delivered at both term and at preterm were included [20,25,33-36,39]. In the other 11 studies (52%), it was not reported whether women delivered at term or preterm [21-24,26-29,32,37,38]. The follow-up period of the included studies varied from 5 months to 52 years. An overall mean weighted follow-up was not calculated because the follow-up periods in the different studies were reported as means (±SD) or medians (ranges/interquartile range).

Biomarkers for inflammation

ICAM and VCAM [24,25,27,32,33,36].

Five studies with a total of 534 cases and 264 controls were able to be included in metaanalyses on ICAM [24,27,32,33,36], which showed no significant difference in mean ICAM levels in women with a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancy (mean difference, 11.04 ng/mL; 95% confidence interval [CI], -12.10 to 34.18; P = 0.35). The test heterogeneity observed was significant (P = 0.04, I2 = 61%) (**figure A**). One study described a higher median ICAM level [25] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

Three studies with a total of 116 cases and 106 controls were able to be included in metaanalyses on VCAM, which showed no significant difference in mean VCAM levels in women with a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancy (mean difference, 68.72 ng/mL; 95% CI, -150.86 to -288.29). The test heterogeneity observed was significant (P<0.00, I2 = 97%) (**figure B**). One study described a higher median VCAM level [25] in women with a history of hypertensive pregnancy disorders compared to women with an uncomplicated pregnancy.

Two studies described higher mean IL-6 levels [27,33], and 1 study described a higher median IL-6 level [31] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a lower median IL-6 level [34] in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy. Overall, IL-6 levels were described higher after pregnancy in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.

One study described a higher mean IL-10 level [27] in women with a history of hypertensive pregnancy disorders compared with women with uncomplicated pregnancy.

One study described a higher mean E-selectin level [24] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described the same mean E-selectin level [32] in women with a history of hypertensive pregnancy disorders and women with uncomplicated pregnancy. Two studies described higher median E-selectin levels [25,39] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. Overall, E-selectin levels were described higher after pregnancy in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy.

Figure A. ICAM

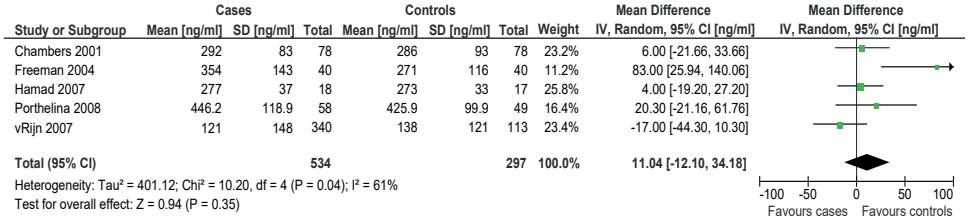
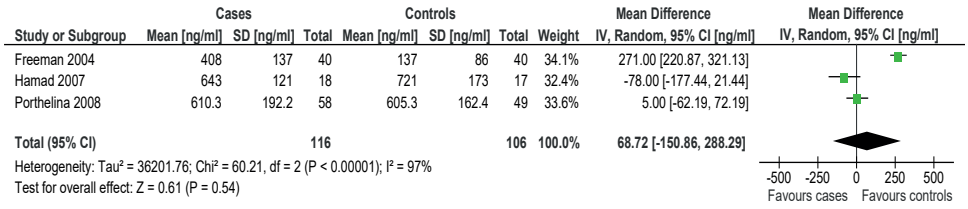


Figure B. VCAM



Biomarkers for thrombosis

Homocysteine, VWF, and fibrinogen [19,20,23,24,26,28,30-35,37]

Five studies with a total of 390 cases and 342 controls could be included in metaanalyses on homocysteine [24,28,30,31,37], which showed higher mean homocysteine levels in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancy (mean difference, 0.77 ng/mL; 95% CI 0.27 to 1.26; P <0.00). The test heterogeneity observed was not significant (P =0.11, I2 = 48%) (**figure C**).

Three studies with a total of 473 cases and 209 controls could be included in metaanalyses on VWF [19,26,32], which showed no significant difference in mean VWF levels in women with a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancy (mean difference, 0.06 ng/mL; 95% CI -0.05 to 0.17; P = 0.28). The test heterogeneity observed was not significant (P = 0.47, I2 = 0%) (**figure D**). Two studies described higher VWF median levels [23,34] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

Four studies with a total of 778 cases and 319 controls could be included in metaanalyses on fibrinogen [20,26,32,33] which showed no significant difference in mean fibrinogen levels in women with a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancy (mean difference, 0.28 g/L; 95% CI -0.02 to 0.59; P = 0.07). The test heterogeneity observed was significant (P = 0.02, I2 = 70%) (**figure E**).

Two studies described higher median fibrinogen levels [23,35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

Two studies described higher mean cellular fibronectin levels [19,20] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One

Figure C. Von Willebrand Factor (VWF)

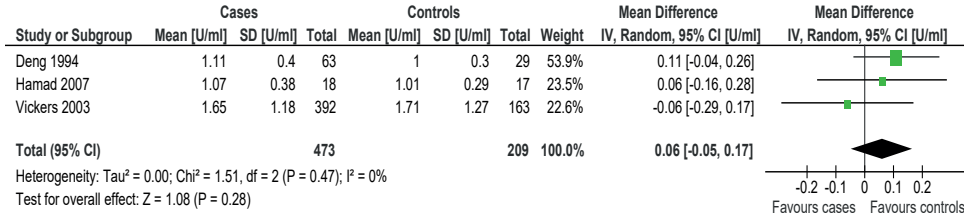
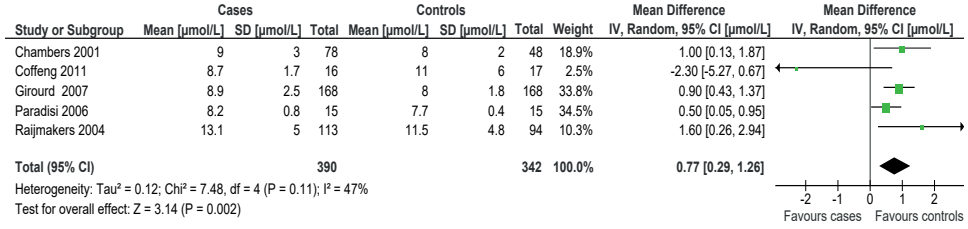


Figure D. Homocysteine



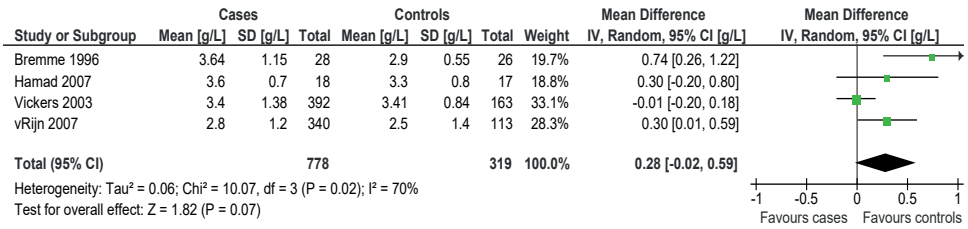
study described a higher mean endothelin levels [21] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described the same mean endothelin level [22] in women with a history of hypertensive pregnancy disorders and women with uncomplicated pregnancy.

One study described a higher mean D-dimer level [20] and 1 study described a higher median D-dimer level [35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

One study described a higher mean PAI-1 level [20] and three studies described higher median PAI-1 levels [23,31,32] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a lower mean PAI-1 level [35] in women with a history of hypertensive pregnancy disorders compared with women with uncomplicated pregnancy.

One study described a higher mean tPA level [32] and 2 studies described higher median tPA levels [23,35] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

Figure E. Fibrinogen



Biomarkers for angiogenesis

VEGF, sFLT-1, and TNF-a [27, 29, 31, 38, 39]

Two studies described higher median VEGF levels [29,39] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

One study described a higher mean sFlt level [29], and 1 study describes higher median sFlt level [39] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy.

One study described a higher mean TNF-a level [27], and 1 study described a higher median TNF-a level [38] in women with a history of hypertensive pregnancy disorders compared to women with uncomplicated pregnancy. One study described a lower median TNF-a level [31] in women with a history of hypertensive pregnancy disorders compared with women with uncomplicated pregnancy.

COMMENT

In this review and metaanalysis, we found that most nonclassic cardiovascular biomarkers were higher in women with a history of hypertensive pregnancy disorders compared to women

with a history of uncomplicated pregnancies in the areas of inflammation, thrombosis, and angiogenesis. Homocysteine was the only biomarker that was significantly higher in women with

a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancies.

This is the first review and metaanalyses that focused on nonclassic cardiovascular biomarkers in women with a history of hypertensive pregnancy disorders. We used a wide spectrum of search terms to evaluate the most important nonclassic cardiovascular biomarkers. The study selection was carried out without language restrictions, and attention was paid to quality assessment by using scoring lists and evaluation by multiple investigators, preventing selection bias and publication bias.

This review and metaanalyses shows higher levels of nonclassic cardiovascular biomarkers in women with a history of hypertensive pregnancy disorders. These elevated biomarkers suggest endothelial activation in hypertensive pregnancy disorders and cardiovascular disease, inclining toward a shared pathophysiology. Our metaanalyses suggest an additional value of one specific biomarker, homocysteine, in the cardiovascular risk assessment.

Guidelines advise treatment in women with elevated cardiovascular risk scores and unfavorable classic cardiovascular risk factors, such as hypercholesterolemia or diabetes, to prevent cardiovascular disease later in life [40,41]. However, until now, no evidence exists that treatment of nonclassic cardiovascular risk factors is effective in the prevention of cardiovascular disease in women [41]. An example is the lack of evidence that, in the case of elevated homocysteine, folic acid supplementation can result in reduction of cardiovascular events [42].

This review has some limitations. First, because of the small number of studies, we were not able

to separately analyze women with a history of gestational hypertension and women with a history of preeclampsia, which may have different pathophysiology [43]. Second, studies did not distinguish between severe and non-severe disease and between preterm and term hypertensive pregnancy disorders, which may also differ pathophysiologic [44]. Third, follow-up time after pregnancy differed between studies. Fourth, both premenopausal and postmenopausal subjects were included in the studies reviewed. Postmenopausal women have a higher cardiovascular disease risk compared to premenopausal women. Thus, post menopause may have confounded our results, although studies that describe only premenopausal women seem to show comparable elevated levels of nonclassical biomarkers in women with a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancy remained.

For thrombotic biomarker homocysteine, we found a significantly higher level in our metaanalyses for women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies. Homocysteine is a biomarker that is linked to the development of atherosclerosis, inflammation, and endothelium injury [45,46]. A large review conducted in 2002 [47] concluded that an increase in fasting plasma homocysteine is associated with an increase in the incidence of ischemic heart disease and an increase in the incidence of stroke.

Homocysteine is a marker for not only cardiovascular disease but also for hypertensive pregnancy disorders [48]. A recent study included homocysteine in an early prediction model for preeclampsia.

[49]. This study concluded that higher levels of homocysteine, in combination with elevation of other biomarkers, in the first trimester of pregnancy could predict the onset of the hypertensive pregnancy disorders later in pregnancy.

In our review, we included homocysteine levels after hypertensive pregnancy disorders. In 2 studies on homocysteine, it is not completely clear whether the results included fasting homocysteine levels [28,31]. Because homocysteine levels can be influenced by oral intake, this could disturb the results of this metaanalyses. The higher levels of homocysteine after a pregnancy complicated by hypertension can result from already present endothelial alteration or persistent endothelial alteration after complicated pregnancy. However, the impact of this finding and clinical consequences are unknown. The effectiveness of lowering of homocysteine levels, by folate acid or vitamin supplementation, to prevent cardiovascular disease has been investigated in several studies [50]. However, a Cochrane Review published in 2013 [42], failed to show evidence to sustain this.

For inflammatory biomarkers ICAM and VCAM, we found no significant differences in levels in our metaanalyses in women with a history of hypertensive pregnancy disorders compared to women with a history of uncomplicated pregnancies. An increase in systemic inflammation can be interpreted as either a cause or a result of atherogenesis in cardiovascular disease or both. Systemic inflammation induces a heightened state of cardiovascular activity, endothelium dysfunction, and induction of adhesion molecules on endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall. This inflammatory process results in macrophage activation with the production of cytokines and other inflammatory biomarkers. These inflammatory biomarkers include ICAM, VCAM, IL-6 and IL-10.

We expected higher levels of inflammatory biomarkers in women with a history of hypertensive

pregnancy disorders compared with women with a history of uncomplicated pregnancies because the inflammatory process is an important part of the pathophysiology of both hypertensive pregnancy disorders as of cardiovascular disease [51,52]. However, we found higher levels only for women with a history of hypertensive disorders in the included articles but not a significant difference in our metaanalyses. Limited sample size might account for this.

For thrombotic biomarkers fibrinogen and VWF, we found no significant differences in our meta-analyses in women with a history of hypertensive pregnancy disorders compared with women with a history of uncomplicated pregnancies. Biomarkers for thrombosis indicate over activation of thrombotic reactions without any blood vessel injury and may result in reduced blood flow, reduced perfusion, and finally cardiovascular disease. In this review, we described established biomarkers for thrombosis in women with a history of hypertensive pregnancy disorders. Most of these biomarkers are known to be elevated in women with preeclampsia and are even used in the early prediction of preeclampsia [52,53]. It has been suggested that thrombosis might be a shared pathophysiological pathway, partly explaining the link between hypertensive pregnancy disorders and cardiovascular disease later life. However, we did not find strong evidence for this in our present review.

Conclusion

Women with a history of hypertensive pregnancy disorders show significantly higher levels of homocysteine compared to women with a history of uncomplicated pregnancy. For other biomarkers of inflammation, thrombosis and angiogenesis, we found no significant increases. These findings suggest impaired endothelial function that persists after or is even already present before hypertensive pregnancy disorders.

Table 1. Characteristics of Included Studies in Review and Meta-analysis

Study, *country*	**Study design**	**Exposure**	**Parity index pregnancy** NP: nullipara, MP: mutipara	**Mean gestational age (weeks) index pregnancy**	**Preterm and/or term pregnancy**	**Cases no.**	**Controls no.**	**Follow up period (years)**	**Non-classic Cardiovascular Marker described**
1. Deng 1994*, *Sweden*[19]	Prospective Cohort	PE	NP+MP	Not reported	T	63	29	1 (5-15months)	VWF, fibronectin (means)
2. Bremme 1996*, *Sweden*[20]	Retrospective CaseControl	PE	NP+MP	Severe PE 33 Mild PE 35	PT+T	42	26	1 (6-15months)	Fibronectin, Fibrinogen, PAI-1, Ddimer (means)
3. Laivuori 1997, *Finnland*[21]	Retrospective CaseControl	PE	Not reported	Not reported	Not reported	22	22	Cases 16.9 Controls 17.0	Endothelin (means)
4. Barden 1999, *Australia*[22]	Retrospective CaseControl	PE	NP+ MP	Not reported	Not reported	62	84	0.5 (6months)	Endothelin (means)
5. He 1999, *Sweden*[23]	Retrospective CaseControl	PE	NP+MP	Not reported	Not reported	24	23	Range:2-5	Fibrinogen, VWF, PAI-1, tPA (medians)
6. Chambers 2001*, *England*[24]	Prospective CaseControl	PE	NP+MP	Not reported	Not reported	78	48	Mean:3	Homocysteine, E-selectin, ICAM (means)
7. Sattar 2003, *Scotland*[25]	Retrospective Cohort	PE	NP	Cases 36 Controls 40	PT+T	40	40	Range:18-28	ICAM, VCAM, E-selectin (medians)
8. Vickers 2003*, *Scotland*[26]	Prospective Cohort	PE+PIH	NP	Not reported	Not reported	392+297	163	Range:33-52	Fibrinogen, VWF (means)

Table 1. Continued

9. Freeman 2004*, *Scotland*[27]	Retrospective CaseControl	PE	NP	Not reported	Not reported	40	40	Mean: 19.8 (cases), 19.9 (controls)	ICAM, VCAM, IL-6, IL-10, TNF-α (means)
10. Raijmakers 2004*, *Netherlands*[28]	Retrospective CaseControl	PE	NP+MP	Not reported	Not reported	113	94	2 (28months)	Homocysteine (means)
11. Wolff 2004, *USA*[29]	Retrospective CaseControl	PE	NP	Not reported	Not reported	29	32	2 (18±7.9 months)	sFlt-1 (means), VEGF (medians)
12. Paradisi 2006*, *Italy*[30]	Prospective Cohort	PIH	NP+MP	Cases 37.9 Controls 39.2	T	15	15	>1 (20months)	Homocysteine (means)
13. Girourd 2007*, *Canada*[31]	Prospective Cohort	PE+PIH	NP+MP	Cases 38.8 Controls 39.4	T	168 63 +105	168	Mean: 7.8	Homocysteine (means) IL-6, PAI-1, TNF-α (medians)
14. Hamad 2007*, *Sweden*[32]	Retrospective CaseControl	PE	NP	Not reported	Not reported	18	17	1 (15months)	Fibrinogen, VWF, tPA, ICAM, VCAM, E-selectin (means) PAI-1(medians)
15. v Rijn 2007*, *Netherlands*[33]	Retrospective CaseControl	PE	NP	Cases 29.9 Controls 40.0	PT+T	340	113	0.5 (>6months)	Fibrinogen, IL-6, ICAM, VWF (means)
16. Lampinen 2008, *Finnland*[34]	Retrospective CaseControl	PE	NP+MP	Cases 33 Controls 40	PT+T	28	20	Range:5-6	IL-6, VWF (medians)

Table 1. Continued

17. Portelinha 2008, *Portugal*[35]	Retrospective CaseControl	PE	Not reported	Cases 35 Controls 39	PT + T	65	54	Mean: 6	PAI-1 (means) Ddimer, Fibrinogen, tPA (medians)
18. Porthelina 2008*, Portugal[36]	Retrospective CaseControl	PE	NP	Cases 34 Controls 39	PT+T	58	49	Mean: 6	VCAM, ICAM (means)
19. Coffeng 2011*, *Netherlands*[37]	Retrospective CaseControl	PE	NP+MP	Not reported	Not reported	16	17	Median: 4	Homocysteine (means)
20. Stepan 2011, *Germany*[38]	Prospective Cohort	PE	Not reported	Not reported	Not reported	37	37	0.5 (6months)	TNFα (medians)
21. Gaugler 2012, *Netherlands*[39]	Retrospective CaseControl	PE	NP+MP	Cases 22.8 Controls 40.2	PT+T	16	18	Median:9.4 (cases) 9.7 (controls)	sFlt , VEGF, E-selectin (medians)

*Studies included in meta-analyses

REFERENCES

1. Burell G, Granlund B. Women's hearts need special treatment. Int J Behav Med 2002;9: 228-42.
2. Stramba-Badiale M, Fox KM, Priori SG, et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. Eur Heart J 2006;27: 994-1005.
3. Douglas PS, Ginsburg GS. The evaluation of chest pain in women. N Engl J Med 1996;334: 1311-5.
4. Vaccarino V, Badimon L, Corti R, et al. Ischaemic heart disease in women: are there sex differences in pathophysiology and risk factors? Position paper from the Working Group on Coronary Pathophysiology and Microcirculation of the European Society of Cardiology. Cardiovasc Res 2011;90:9-17.
5. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM. Chest pain in women: clinical, investigative, and prognostic features. BMJ 1994;308:883-6.
6. Arslanian-Engoren C. Women's risk factors and screening for coronary heart disease. J Obstet Gynecol Neonatal Nurs 2011;40: 337-46; quiz 346-7.
7. Berks D, Hoedjes M, Raat H, Duvekot J, Steegers E, Habbema J. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013;120:924-31.
8. Sattar N, Greer A. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 2002;325: 157-60.
9. Buurma AJ, Turner RJ, Driessen JH, et al. Genetic variants in pre-eclampsia: a meta-analysis. Hum Reprod Update 2013;19:289-303.
10. Hermes W, Ket JC, van Pampus MG, et al. Biochemical cardiovascular risk factors after hypertensive pregnancy disorders: a systematic review and meta-analysis. Obstet Gynecol Surv 2012;67:793-809.
11. Ge Y, Wang TJ. Identifying novel biomarkers for cardiovascular disease risk prediction. J Intern Med 2012;272:430-9.
12. Gilstrap LG, Wang TJ. Biomarkers and cardiovascular risk assessment for primary prevention: an update. Clin Chem 2012;58: 72-82.
13. Dotsenko O, Chackathayil J, Patel JV, Gill PS, Lip GY. Candidate circulating biomarkers for the cardiovascular disease continuum. Curr Pharm Des 2008;14:2445-61.
14. Masoura S, Kalogiannidis IA, Gitas G, et al. Biomarkers in pre-eclampsia: a novel approach to early detection of the disease. J Obstet Gynaecol 2012;32:609-16.
15. Baumann MU, Bersinger NA, Surbek DV. Serum markers for predicting pre-eclampsia. Mol Aspects Med 2007;28:227-44.

16. Ge Y, Wang TJ. Identifying novel biomarkers for cardiovascular disease risk prediction. J Intern Med 2012;272:430-9.

17. Gilstrap LG, Wang TJ. Biomarkers and cardiovascular risk assessment for primary prevention: an update. Clin Chem 2012;58: 72-82.

18. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in metaanalyses. BMJ 2003;327:557-60.

19. Deng L, Bremme K, Hansson LO, Blombäck M. Plasma levels of von Willebrand factor and fibronectin as markers of persisting endothelial damage in preeclampsia. Obstet Gynecol 1994;84:941-5.

20. Bremme K, Blombäck M. Hemostatic abnormalities may predict chronic hypertension after preeclampsia. Gynecol Obstet Invest 1996;41:20-6.

21. Laivuori H, Kaaja R, Rutanen EM, Viinikka L, Ylikorkala O. Evidence of high circulating testosterone in women with prior preeclampsia. J Clin Endocrinol Metab 1998;83:344-7.

22. Barden AE, Beilin LJ, Ritchie J, Walters BN, Michael C. Does a predisposition to the metabolic syndrome sensitize women to develop preeclampsia? J Hypertens 1999;17:1307-15.

23. He S, Silveira A, Hamsten A, Blombäck M, Bremme K. Haemostatic, endothelial and lipoprotein parameters and blood pressure levels in women with a history of preeclampsia. Thromb Haemost 1999;81:538-42.

24. Chambers JC, Fusi L, Malik IS, Haskard DO, De Swiet M, Kooner JS. Association of maternal endothelial dysfunction with preeclampsia. JAMA 2001;285:1607-12.

25. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and novel risk factor parameters in women with a history of preeclampsia. Hypertension 2003;42:39-42.

26. Vickers M, Ford I, Morrison R, et al. Markers of endothelial activation and atherothrombosis in women with history of preeclampsia or gestational hypertension. Thromb Haemost 003;90: 1192-7.

27. Freeman DJ, McManus F, Brown EA, et al. Short- and long-term changes in plasma inflammatory markers associated with preeclampsia. Hypertension 2004;44:708-14.

28. Raijmakers MT, Roes EM, Zusterzeel PL, Steegers EA, Peters WH. Thiol status and antioxidant capacity in women with a history of severe pre-eclampsia. BJOG 2004;111:207-12.

29. Wolf M, Hubel CA, Lam C, et al. Preeclampsia and future cardiovascular disease: potential role of altered angiogenesis and insulin resistance. J Clin Endocrinol Metab 2004;89: 6239-43.

30. Paradisi G, Biaggi A, Savone R, et al. Cardiovascular risk factors in healthy women with previous gestational hypertension. J Clin Endocrinol Metab 2006;91:1233-8.

31. Girouard J, Giguère Y, Moutquin JM, Forest JC. Previous hypertensive disease of pregnancy is associated with alterations of markers of insulin resistance. Hypertension 2007;49:1056-62.

32. Hamad RR, Eriksson MJ, Silveira A, Hamsten A, Bremme K. Decreased flowmediated dilation is present 1 year after a preeclamptic pregnancy. J Hypertens 2007;25: 2301-7.

33. van Rijn BB, Franx A, Steegers EA, et al. Maternal TLR4 and NOD2 gene variants, proinflammatory phenotype and susceptibility to early-onset preeclampsia and HELLP syndrome. PLoS One 2008;3:e1865.

34. Lampinen KH, Rönnback M, Groop PH, Kaaja RJ. A relationship between insulin sensitivity and vasodilation in women with a history of preeclamptic pregnancy. Hypertension 2008;52:394-401.

35. Portelinha A, Cerdeira AS, Belo L, et al. Haemostatic factors in women with history of preeclampsia. Thromb Res 2009;124:52-6.

36. Portelinha A, Belo L, Tejera E, Rebelo I. Adhesion molecules (VCAM-1 and ICAM-1) and C-reactive protein in women with history of preeclampsia. Acta Obstet Gynecol Scand 2008;87:969-71.

37. Coffeng SM, Blaauw J, Souwer ET, et al. Skin autofluorescence as marker of tissue advanced glycation end-products accumulation in formerly preeclamptic women. Hypertens Pregnancy 2011;30:231-42.

38. Stepan H, Philipp A, Roth I, et al. Serum levels of the adipokine chemerin are increased in preeclampsia during and 6 months after pregnancy. Regul Pept 2011;168:69-72.

39. Gaugler-Senden IP, Tamsma JT, van der Bent C, Kusters R, Steegers EA, de Groot CJ. Angiogenic factors in women ten years after severe very early onset preeclampsia. PLoS One 2012;7:e43637.

40. Mosca L. Guidelines for prevention of cardiovascular disease in women: a summary of recommendations. Prev Cardiol 2007;10(Suppl 4):19-25.

41. Perk J, De Backer G, Gohlke H, et al. European Association for Cardiovascular Prevention and Rehabilitation (EACPR). European guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Int J Behav Med 2012;19:403-88.

42. Martí-Carvajal AJ, Solà I, Lathyris D, Karakitsiou DE, Simancas-Racines D. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev 2013;1:CD006612.

43. Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. Am J Epidemiol 1998;147: 1062-70.

44. Raymond D, Peterson E. A critical review of early-onset and late-onset preeclampsia. Obstet Gynecol Surv 2011;66:497-506.

45. Bogdanski P, Miller-Kasprzak E, Pupek-Musialik D, et al. Plasma total homocysteine is a determinant of carotid intima-media thickness and circulating endothelial progenitor cells in patients with newly diagnosed hypertension. Clin Chem Lab Med 2012;50: 1107-13.

46. Ruijter W, Westendorp RG, Assendelft WJ, et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based bservational cohort study. BMJ 2009;338:a3083.

47. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 288:2015- 22.

48. Demir B, Demir S, Pasa S, et al. The role of homocysteine, asymmetric dimethylarginine and nitric oxide in pre-eclampsia. J Obstet Gynaecol 2012;32:525-8.

49. Masoura S, Kalogiannidis IA, Gitas G, Goutsioulis A, Koiou E, Athanasiadis A, Vavatsi N. Biomarkers in pre-eclampsia: a novel approach to early detection of the disease. J Obstet Gynaecol 2012;32:609-16.

50. Smulders YM, Blom HJ. The homocysteine controversy. J Inherit Metab Dis 2011;34:93-9.

51. Fontes JD, Yamamoto JF, Larson MG, et al. Clinical correlates of change in inflammatory biomarkers: the Framingham Heart Study. Atherosclerosis 2013;228:217-23.

52. Forest JC, Charland M, Massé J, et al. Candidate biochemical markers for screening of preeclampsia in early pregnancy. Clin Chem Lab Med 2012;50:973-84.

53. Aref S, Goda H. Increased VWF antigen levels and decreased ADAMTS13 activity in preeclampsia. Hematology 2013;18:237-41.